

Center Reflections

A monthly publication highlighting activities at the W.M. Keck Foundation Center for Molecular Structure

California State University Fullerton

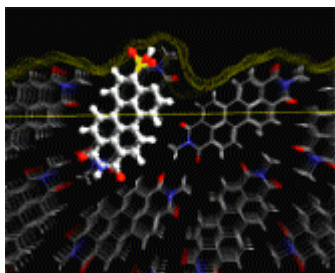
Volume 2, Issue 5

Oct/Nov 2000

Solving Crystal Structures of Materials

Katriona Knapman

Crystallization affects the properties and processing of materials. The crystal structure of a material is the arrangement of atoms or molecules in the solid material. Knowing what the crystal structure is helps to explain why a material or chemical behaves in a certain way. Changing or controlling the crystal structure is one way of changing the properties of a system.



Minimum energy position of a tailor made additive on the (011) crystal face of perylene red.

The crystal structure controls properties such as colour, bioavailability, solubility, density, and shock sensitivity. The bulk crystal shape, or morphology, which is related to the underlying structure, also affects many of these properties and impacts processing and formulation.

All sorts of inorganic and organic materials are affected by crystallization, from cements to pigments to drugs. The colour of pigments and the bioavailability of drugs can be affected by the manner in which molecules crystallize.

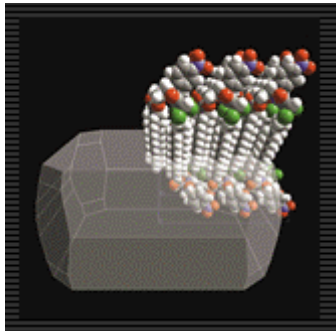
The way in which crystalline materials grow is also important to many industries. For example, the formation of scale on water pipes at oil wells can be a big problem in the oil industry. The scale formation is a crystalline process, knowing how the crystals grow helps researchers to design additives that inhibit the growth of the most active crystal faces of the scale.

Crystal structure is generally solved by diffraction. Single crystal X-ray diffraction is a far more reliable method, but requires that a large and pure enough crystal of the material be grown in the lab. It can be difficult and time consuming to grow large crystals of some materials, so the solving of crystal structure remains a difficult task. Powder X-ray diffraction produces a spectrum from ground up crystalline material. It is easier to produce experimentally, but it is hard to determine the crystal structure from a powder diffraction pattern, and a lot of analysis is required to come up with reliable results.

Molecular modelling can help to solve crystal structure in a number of ways:

- It can help to interpret a powder diffraction pattern and thereby solve a crystal structure.
- It can predict the ways in which a certain molecular structure might crystallize, helping scientists to predict whether they have found all of the possible crystal structures, or polymorphs, for a molecule.
- It can also help scientists to model how a crystalline material will grow, and let them predict the effect of an additive on crystal growth.

Crystal Structure from Powder Diffraction



Predicted crystal morphology of a pharmaceutical, showing the orientation relative to the molecular packing of the crystalline drug.

Although it is often difficult to carry out single crystal X-ray diffraction, high-quality powder patterns still contain useful structural information. A number of techniques are available to index the pattern to derive cell parameters [1,2]. Knowledge of systematic absences can help determine which space groups are most likely for that structure. These two pieces of information, combined with the contents of the asymmetric

unit, are necessary to determine the crystal structure directly from the experimental powder pattern.

A program called C2 PowderSolve is available from Molecular Simulations Inc. that helps researchers to determine crystal structure from powder diffraction data. Given an indexable high-quality powder pattern and the molecular structure of the compound, C2 Powder Solve involves the following methods to determine the three-dimensional crystal structure:

- The C2 Powder Indexing tools are used to determine the cell parameters and lattice class by indexing the experimental powder pattern
- The C2 Powder Fit module refines the cell parameters, peak shape, and background parameters using a modified Pawley procedure
- The C2 Powder Solve module performs a search of possible arrangements and conformations of the molecular fragments in the unit cell, then proposes a structure whose simulated powder spectrum matches the experimental one as closely as possible [3].

C2 PowderSolve has been used to determine the crystal structure of tetracycline hydrochloride, a compound that has previously served in a blind test to assess the efficiency of methods for structure determination from powder diffraction data. The structure solution of tetracycline hydrochloride illustrates the huge potential of powder diffractometry combined with modern software tools.

Read the full case study for more information:

http://www.msi.com/materials/cases/an_roundrobin.html

Polymorph Prediction

Polymorphism is the ability of a chemical to crystallize into more than one crystal form. Pharmaceuticals, agrochemicals, pigments, dyes, specialty chemicals and explosives are all, at some stage during the manufacturing process, organic crystalline materials. Polymorphism will affect these products during down-stream development and formulation.

The existence of different crystal forms impacts on key properties such as shelf-life, vapor pressure, solubility, bioavailability, morphology, density and shock sensitivity. It is vital that researchers involved in the formulation of crystalline products can select the polymorph with the correct properties, and anticipate problems such as the unwanted crystallization of other polymorphs. In order to do this they need to establish the likely polymorphic forms. This knowledge is also important for patenting and registration purposes.

It is often impossible or impractical to use single crystal X-ray diffraction to determine the possible polymorphs for a given molecule. Besides the difficulties inherent in X-ray crystal diffraction, the researcher may also want to know about polymorphs that have not yet been synthesized. To find the possible polymorphs the researcher needs to piece together experimental results - such as powder diffraction patterns - and computational evidence, such as lattice energy calculations. Much effort is needed to model trial crystal structures. The process is painstaking, time-consuming and often unrewarding.

Computational polymorph prediction takes the molecular structure of an organic compound and predicts possible polymorphs. This technology enables research chemists to move ahead from an identified lead com-

pound to characterization, property prediction, and control of polymorphic structures.

Growth Inhibition and Additive Design

The use of additives to control or inhibit the growth of organic crystals is of vital importance in the chemical and pharmaceutical industries. Preventing or modifying the growth of inorganic crystalline phases - such as scales, cements, and the metal oxides produced by corrosion - is equally important in the transport and production of chemicals, petroleum and its derivatives, and in the functioning of water-containing systems such as pipelines and air conditioning. Scientists designing speciality additives to address these issues are increasingly using rational molecular design processes - such as molecular modeling - to reduce the amount of trial-and-error experimentation that their work involves.

Morphology control is achieved by designing additives that selectively inhibit the growth of particular faces. Modeling is used to find growth inhibiting additives which bind more strongly to one face than another, or which alter the attachment energy at a particular face once they are incorporated within a crystal lattice.

The first step is often to build models of crystalline structure and predict morphology. This indicates the principal crystal faces upon which growth is focused. Atomistic models of these crystal faces can be built in a molecular modeling environment.

Once the connection between atomistic structure and morphology is established, the next question is how to alter the surface structure to control the morphology. Tailor-made additives that bind to the crystal faces are often used to do this. The design of ad-

ditives to control crystal growth is facilitated by molecular modeling.

The interaction of the surfaces and molecules of interest can then be investigated. There are excellent automated tools available for finding the binding sites and conformations of molecular species on surfaces. The binding energies and dynamic behavior (indicating stability) of these systems can then be investigated using molecular mechanics methods [4].

References

1. P.E. Werner, L. Eriksson and M. Westdahl, *J. Appl. Cryst.*, **18**, 367 (1985).
2. A. Boulton and D. Louer, *J. Appl. Cryst.*, **24**, 987, (1991).
3. G. E. Engel, S. Wilke, O. König, K. D. M. Harris and F. J. J. Leusen, *J. Appl. Cryst.* **32**, 1169-1179, (1999).
4. Coveney P.V., Humphries W., *J. Chem. Soc., Faraday Trans.*, **92**(5), 831, (1996).

Reprinted with permission by The Alchemist
copyright © 1997-2000 ChemWeb Inc.

[All rights reserved](#)

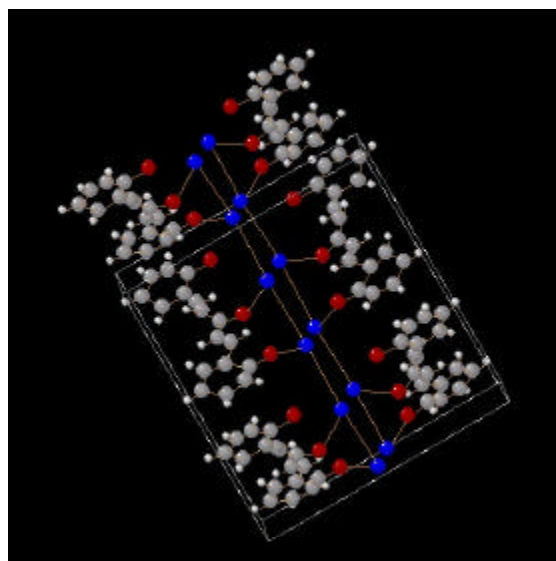
Cytotoxicity of Some a,b- Unsaturated Ketones

CSU Hayward

At California State University Hayward, the main research of Professor Emeritus Richard E. Bozak is characterized by simple syntheses of novel organometallic compounds and how they might be biologically active.

Among the molecules made by Bozak and his group of students are ferrocenylrhodanine- tested as a herbicide, ferrocenylmethanol using Baker's Yeast, and a 1,1'-diacetylferrocene degradation product- effective against mouse leukemia cells. Precise atomic coordinates and molecular geometries obtained by x-ray diffraction are vital to our understanding of the chemical properties of these compounds.

Jeff Madrid, a research student at CMoIS with Katherine Kantardjieff, has been working to elucidate the structures of two cytotoxic ketones. The first of these, shown below, forms twinned crystals. Work is in progress to refine the structure from the twinned data as well as to grow better crystals. The second compound forms highly mosaic crystals, which undergo an interesting phase transition when flash cooled. Better crystallization conditions are being explored.



Bozak received his B.S. degree in chemistry from the University of Washington in 1956, where he did research with Ken Wiberg. He went on to receive his Ph.D. from U.C. Berkeley under professor W.G. Dauben in 1959. He then became a "pioneer" postdoc in the former Soviet Union until late 1960. During part of this time, he was "starosta" of the small American contingent. After a further postdoc with K.L. Reinhart in Urbana, Illinois, Bozak worked for Shell Chemical for two years in the San Francisco Bay area.

After joining the faculty at Hayward in 1964, Bozak promptly began lab research with local students. An early development was the ferrocene/acetyl ferrocene chroma-

tography experiment, variations of which are still used in almost all organic laboratory manuals. Bozak has wedded his commitment to keeping an undergraduate research program while maintaining good teaching standards as required at a predominantly undergraduate college.

Bozak has authored over 30 papers in refereed publications, and he has given numerous scientific talks from Rome to Tokyo. An academic hobby of Bozak's is the study of the history of the development of the atomic bomb. Professor Bozak and his wife, Pat, who enjoy traveling the world, live in Dublin, CA. His daughter, Kristin R. Bozak, is Professor of Biology at Cal Poly Pomona.

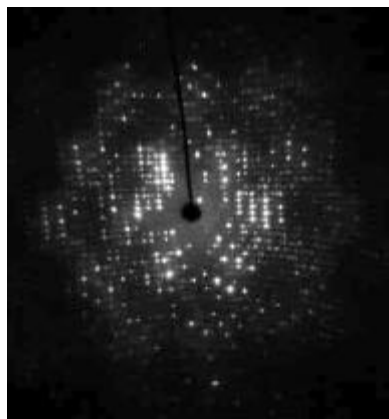
Detectors Used in X-ray Diffraction

CMoIS

This article describes briefly the different types of detectors available for x-ray diffraction experiments. Detectors vary, depending on the physics involved in detecting the scattered x-ray photons and recording the intensity of scattering, the sensitivity, the dynamic range, and the spacial resolution.

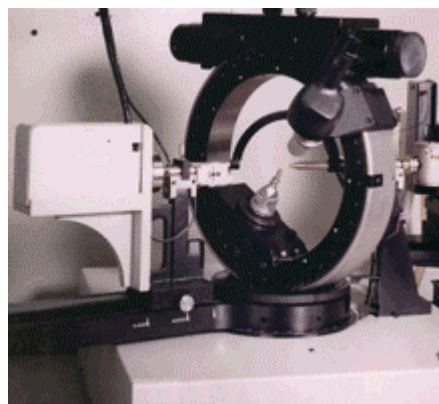
Film (2D)

Film for x-ray data collection is double coated photographic film. It is not truly a proportional counter, and it has a limited dynamic range. Film is cumbersome and time-consuming to process. Thus, it is rarely used, except for teaching purposes using x-ray cameras. An example of a film image is shown at the top of the next column.



Scintillation (1D)

A scintillation or 'point' detector, which is shown on the next page, produces optical photons when struck by ionizing radiation. A PMT tube is then used to detect the light. Point detectors have been used almost exclusively on conventional x-ray sources for small molecule data collection, and it typically takes several days to collect a hemisphere of data. The crystal must be 'oriented' prior to commencing data collection.

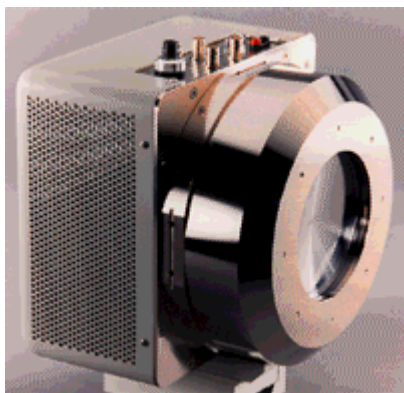


Multi-wire (2D)

Multi-wire detectors are used on conventional x-ray sources for crystallographic studies of large molecules, to examine specimens that decay rapidly during analysis, and for powder diffraction. This type of

detector is an imaging proportional counter. The detector is filled with pressurized xenon gas (4 bar = 400,000N/m²) and is capable of determining X and Y positions of x-rays that enter its imaging area.

Scattered x-rays from a crystal enter the detector through a beryllium window with little curvature. Atoms of xenon are ionized by incident x-rays, producing a shower of charged particles each time an x-ray passes through the gas. Charged particles are attracted electrically to a multi-wire electrode assembly in the detector (500µm apart) with which they interact to generate electrical signals indicative of X-Y position. From the electrode assembly, electrical signals are routed to a preamplifier in the detector, then output to a computer. Multi-wire detectors are very sensitive and fast. Counting rates are limited, however, due to charge build-up and limits in the processing electronics.



Preliminary protein structure studies and powder diffraction studies at CMoIS are conducted on a multiwire area detector like the one shown above, mounted on a Cu rotating anode x-ray source.

CCD(2D)

A CCD detector consists of a charge-couple device chip of much higher quality than that found in video cameras. It is a solid-state imager with an array of potential wells

holding charge, which can be read out in two dimensions. Each pixel of the image behaves like an independent detector. A thin phosphor screen is used to convert x-rays into visible light, which is coupled via lenses, image intensifiers and/or fiber optics to the CCD, which records the light signal. For maximum transmission efficiency, the chip can be bonded directly to a fiber optic taper.

A CCD is a relatively proportional counter with a wide dynamic range, it is very fast, and it is highly sensitive to signals at short wavelength. This type of detector has remarkable spatial resolution (60µm) at the detector face. An entire hemisphere of data could be collected in 6-12 hours. CCD detectors have revolutionized routine crystallography, and they have been implemented at synchrotrons.

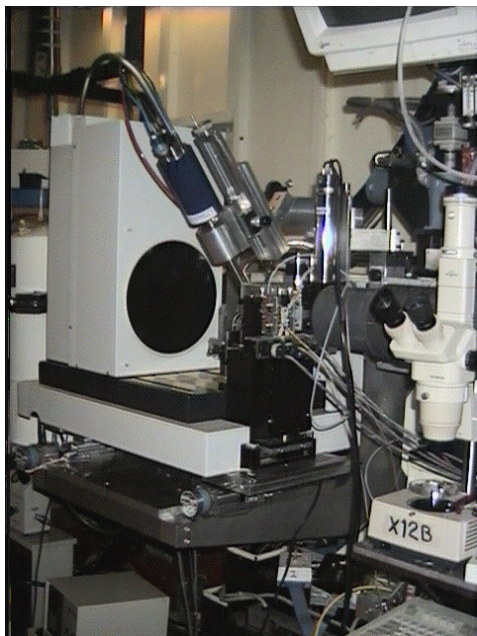


The small molecule diffractometer system at CMoIS uses a CCD detector like the one shown above, mounted on a sealed tube Mo x-ray source.

Image Plate (2D)

An image plate, such as the one shown below, consists of a thin layer of inorganic storage phosphor that has been deposited onto a flat base. X-ray photons excite electrons in the material to higher energy levels. Some of this energy is lost soon after as fluorescent light, but an appreciable amount is retained in color centers. This energy dissipates slowly over several days. The stored

energy is released by exposure to red laser light. The emitted blue light is then measured with a PMT. Image plates are commonly found at synchrotrons.



Websites of Interest

American Crystallographic Association
<http://nexus.hwi.buffalo.edu/aca/index.html>

International Union of Crystallography
<http://www.iucr.org/>

Xtal Nexus Internet Crystallography Software Library and Virtual WWW
<http://www.unige.ch/crystal/stxnews/nexus/index.htm>

CCP14: Collaborative Computational Project Number 14 for Single Crystal and Powder Diffraction (freely available crystallographic software for academia) <http://www.ccp14.ac.uk>

Emerald BioStructures offers products and services in protein X-ray crystallography, specializing in the area of protein crystallization.
<http://www.emeraldbiostructures.com/>

Upcoming Events

September 26, 2000: **San Jose State University** "X-ray Diffraction Studies in a Predominantly Undergraduate Institution". Seminar given by Prof. Katherine Kantardjieff.

October 25 - 28, 2000: **American Chemical Society Western Regional Meeting**, San Francisco, CA.
<http://www.mcs.csu Hayward.edu/~wwwchem/Natmeet.html>

October 28, 2000: **Seaborg Symposium and Medal Dinner**, UCLA. Day-long symposium entitled "Receptors and Human Health". Award dinner follows. Honoree: Daniel Koshland, Editor-in-Chief (1985-1995), *Science*.

November 2-5, 2000: **International Structural Genomics Conference**, Yokohama, Japan.
<http://icsg2000.RIKEN.go.jp/>

December 14 - 19, 2000: **Pacificchem 2000**, Honolulu, Hawaii.
<http://www.acs.org/meetings/pacific2000/>

January 9-11, 2001: **Crystallography for Chemists Workshop**, CSU Fullerton.

January 11-13, 2001: **CSUPERB Symposium**, Cal Poly Pomona.

July 21-26, 2001: **American Crystallographic Association National Meeting**, Los Angeles, CA.
<http://www.hwi.buffalo.edu/ACA/ACA-Annual/LosAngeles/LosAngeles.html>

March 25-28, 2001: **West Coast Protein Crystallography Workshop**, Asilomar, CA.
<http://www.gene.wcpw/>

April 1 - 5, 2001: **American Chemical Society National Meeting**, San Diego, CA.
<http://www.acs.org/meetings/>

April 18-22, 2001: **4th European Protein Symposium**, Paris, France.
<http://www.faseb.org/meetings/ep01/>

August 26 - 30, 2001: **American Chemical Society National Meeting**, Chicago, IL.
<http://www.acs.org/meetings/>

August 6-15, 2002: **International Union of Crystallography Meeting**, Jerusalem, Israel.
<http://www.iucr.org/>

Crystallography for Chemists Workshop

January 9-11, 2001

W.M. Keck Foundation

Center for Molecular
Structure

California State University
Fullerton

Sponsors

Bruker-AXS

Hampton Research

CSUF

CSUPERB

Facilitators

Charles Campana, Bruker - AXS

Katherine Kantardjieff, CSUF

Duncan McRee, TSRI

Bernhard Rupp, LLNL

Robert Sweet, BNL

Joseph Ziller, UCI

Online Registration and Schedule

<http://www-structure.llnl.gov/CCW/CCW.htm>

W.M. Keck Foundation Center for Molecular Structure

Department of Chemistry and Biochemistry

California State University Fullerton

800 N. State College Blvd.

Fullerton, CA 92831

<http://zeppo.fullerton.edu:8080/~kkant/cmols2.html>

Director: Dr. Katherine Kantardjieff
kkantardjieff@fullerton.edu

Staff Scientist: See job posting on website.